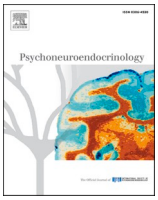
Psychoneuroendocrinology 146 (2022) 105896

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen



Associations between maternal prenatal depression and neonatal behavior and brain function – Evidence from the functional near-infrared spectroscopy

Shan Wang [a,f], Chenxi Ding [a], Chengyin Dou [a], Zeen Zhu [b], Dan Zhang [a], Qiqi Yi [a], Haoyue Wu [a], Longshan Xie [c], Zhongliang Zhu [d], Dongli Song [e,**], Hui Li [a,f,*]

[a] Department of Neonatology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China
[b] Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China
[c] Department of Functional Neuroscience, The First People's Hospital of Foshan (The Affiliated Foshan Hospital of Sun Yat -sen University), Guangdong, China
[d] Key Laboratory of Resource Biology and Biotechnology in Western China, Ministry of Education, Maternal and Infant Health Research Institute and Medical College, Northwestern University, Xi'an, China
[e] Division of Neonatology, Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, CA, USA
[f] Department of Neonatology, the Affiliated Children Hospital of Xi'an Jiaotong University, Xi'an, China

ARTICLE INFO

Keywords:
Prenatal depression
Cortisol
Behavioral development
Neonatal behavior

ABSTRACT

Background: Maternal prenatal depression is a significant public health issue associated with mental disorders of offspring. This study aimed to determine if maternal prenatal depressive symptoms are associated with changes in neonatal behaviors and brain function at the resting state.

Methods: A total of 204 pregnant women were recruited during the third trimester and were evaluated by Edinburgh Postpartum Depression Scale (EPDS). The mother-infant pairs were divided into the depressed group (n = 75) and control group (n = 129) based on the EPDS, using a cut-off value of 10. Cortisol levels in the cord blood and maternal blood collected on admission for delivery were measured. On day three of life, all study newborns were evaluated by the Neonatal Behavior Assessment Scale (NBAS) and 165 infants were evaluated by resting-state functional near-infrared spectroscopy (rs-fNIRS). To minimize the influences of potential bias on the rs-fNIRS results, we used a binary logistic regression model to carry out propensity score matching between the depressed group and the control group. Rs-fNIRS data from 21 pairs of propensity score-matched newborns were used for analysis. The associations between maternal EPDS scores, neonatal NBAS scores, and cortisol levels were analyzed using linear regressions and the mediation analysis models.

Results: Compared to the control group, the newborns in the depressed group had lower scores in the social-interaction and autonomic system dimensions of NBAS ($P < 0.01$). Maternal and umbilical cord plasma cortisol levels in the depressed group were higher ($P < 0.01$) than in the control group. However, only umbilical cord plasma cortisol played a negative mediating role in the relationship between maternal EPDS and NBAS in the social-interaction and autonomic system (β med = −0.054 [−0.115,−0.018] and −0.052 [−0.105,−0.019]. Proportional mediation was 13.57 % and 12.33 for social-interaction and autonomic systems, respectively. The newborns in the depressed group showed decreases in the strength of rs-fNIRS functional connections, primarily the connectivity of the left frontal-parietal and temporal-parietal regions. However, infants in the depressed and control groups showed no differences in topological characteristics of the brain network, including standardized clustering coefficient, characteristic path length, small-world property, global efficiency, and local efficiency ($P > 0.05$). The social-interaction Z-scores had positive correlations with functional connectivity strength of left prefrontal cortex-left parietal lobe ($r = 0.57$, $p < 0.01$) , prefrontal cortex-left parietal lobe - left temporal lobe ($r = 0.593$, $p < 0.01$) and left parietal lobe - left temporal lobe ($r = 0.498$, $p < 0.01$). Autonomic system Z-scores were also significantly positive correlation with prefrontal cortex-left parietal lobe ($r = 0.509$, $p < 0.01$) , prefrontal cortex-left parietal lobe - left temporal lobe ($r = 0.464$, $p < 0.01$), left parietal lobe - left temporal lobe ($r = 0.381$, $p < 0.05$), and right temporal lobe and left temporal lobe ($r = 0.310$, $p < 0.05$).

* Corresponding author at: Department of Neonatology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.
** Corresponding author.
E-mail addresses: dlsongster@gmail.com (D. Song), huili@mail.xjtu.edu.cn (H. Li).

https://doi.org/10.1016/j.psyneuen.2022.105896
Received 10 March 2022; Received in revised form 8 August 2022; Accepted 19 August 2022
Available online 23 August 2022

Conclusion: This study shows that maternal prenatal depression may affect the development of neonatal social-interaction and autonomic system and the strength of neonatal brain functional connectivity. The fetal cortisol may play a role in behavioral development in infants exposed to maternal prenatal depression. Our findings highlight the importance of prenatal screening for maternal depression and early postnatal behavioral evaluation that provide the opportunity for early diagnosis and intervention to improve neurodevelopmental outcomes.

1. Introduction

Maternal prenatal depression is associated with poor neurodevelopment in the offspring that has a lifelong adverse impact on neurocognitive function and mental health (Ruisch et al., 2018, Tuovinen et al., 2018, Van den Bergh et al., 2020). A recent meta-analysis involving 70 studies demonstrated that children born to mothers with prenatal depression had a 1.79-fold increased risk of behavioral difficulties (Madigan et al., 2018). Although much less examined, available evidence shows that altered neurobehaviors are detectable as early as in affected newborns. On the Brazelton Neonatal Behavioral Assessment Scale (NBAS), neonates born to mothers with prenatal depression (in the second or third pregnancy trimester) had less optimal performance in habituation, range of state, and regulation of the state. They showed less alertness, cuddliness, and hand-to-mouth activity and did not have a preference for their mother's face and voice (Field et al., 2006, Figueiredo et al., 2010, Pacheco and Figueiredo, 2012). Prenatal depression has also been associated with delayed fetal and neonatal neurobehavioral maturity manifested as low heart rate variability (DiPietro et al., 2015, Figueiredo et al., 2017).

Prenatal depression affects brain development, especially in brain regions related to affective disorders (O'Donnell and Meaney, 2017, Graham et al., 2020). Recent brain MRI studies have identified the brain structural and functional changes associated with maternal prenatal stress. The most consistent findings are changes in the frontal and temporal lobes, including cortical thinning, reductions in gray matter volume in the limbic system, and increases in amygdala volume (Graham et al., 2020). For example, an MRI study showed a negative correlation between the maternal Edinburgh Postnatal Depression Scale (EPDS) and cortical thickness of preschool-age offspring (Lebel et al., 2016).

Resting-state fMRI (rs-fMRI) measures the temporal synchronization of spontaneous blood-oxygen-level-dependent (BOLD) signal fluctuations in the absence of explicit tasks. Rs-fMRI provides information about spontaneous brain activity and functional connectivity (FC) (Gilmore et al., 2018). Graph theory analytical technique is commonly used to characterize the key properties of the brain network topological patterns, including clustering coefficient, characteristic path length, node degree, efficiency, and small-world properties (Cai et al., 2018). In the developing fetal brain, sequential, coordinated, and hierarchical development of functional brain networks. Specifically, FC involving short-distance connections within primary functional networks (the sensorimotor, visual, and auditory networks) develop first. With the increasing gestation, there is a gradual emergence of cross-hemispheric, cortico-subcortical, and long-range connectivity (e.g., between frontal and temporal lobes) and increases in efficiency and modularity (e.g., FC intensity in the internal frontal and parietal lobes) (Keunen et al., 2017; Gilmore et al., 2018; Edde et al., 2021). Recent brain imaging studies have demonstrated that the neonatal brain's functional networks have small-world properties, which have been observed in the adult brain networks (Anderson et al., 2011, Smyser et al., 2013). This highly overlapped cortical functional organization between adult and fetal indicates that mature functional dynamics have a fetal origin (Turk et al., 2019). At birth, the newborn brains show the existence of primary sensorimotor, auditory, and visual networks similar to adult brains (Gao et al., 2015, Ouyang et al., 2017). Rs-fMRI has been used to characterize the neurodevelopment changes of offspring exposed to prenatal stress. A decrease in ventral prefrontal cortex structural connectivity was observed in 5.8-week-old infants who were prenatally exposed to maternal depression (Posner et al., 2016). Qiu et al. (2015) showed that 6-month-old infants born to mothers with depression during pregnancy had different FC of some brain regions, including the amygdala, the left temporal cortex, insula, bilateral anterior cingulate, medial orbitofrontal and ventromedial prefrontal cortices.

Like fMRI, functional near-infrared spectroscopy (fNIRS), captures changes in brain BOLD signal associated with neuronal activity. However, fNIRS, compared to fMRI, has several advantages; higher temporal resolution (tens of milliseconds), low cost, portability, and relatively higher tolerance of head movement. It can be used at the bedside or in outpatient clinical settings (Benavides-Varela et al., 2011); hence, it is ideal for studying a large cohort of young children. fNIRS has been used to explore the relationship between connectome indicators (e.g., brain functional connectivity (FC), brain asymmetry, and network features) and behavioral performance in children (Hu et al., 2020). A recent study by Kelsey et al. found that the variability of functional network connectivity was associated with individual differences in behavioral temperament across infants (Kelsey et al., 2021).

Transplacental hormone transfer is a potential mechanism mediating prenatal depression and offspring development (Beijers et al., 2014). Prenatal depression actives the maternal hypothalamic-pituitary-adrenal (HPA) axis, leading to increases in cortisol expression and transplacental transfer to the fetus (Seckl and Holmes, 2007; O'Donnell and Meaney, 2017). While placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) protects the fetus from cortisol overexposure during pregnancy (Morsi et al., 2018), impaired 11β-HSD2 activity might result in excessive cortisol crossing the placenta. Elevated levels of cortisol influence fetal development, including brain structures and functions, leading to long-term neurodevelopmental consequences (O'Donnell and Meaney, 2017, Caparros-Gonzalez et al., 2019). Although the effect of maternal cortisol on the developing fetus exposed to maternal stress has been studied extensively (Lautarescu et al., 2020), it's relative mediating impact has not been defined.

To our knowledge, no studies have investigated the correlation between neonatal behaviors (NBAS) and brain FC, despite the strong associations between prenatal depression and abnormal brain development. The studies linking prenatal maternal depression and offspring brain connectivity are limited to infants or older children, leaving a critical gap in knowledge of brain function and behavior in the newborn period, a time the observed abnormalities are attributed to perinatal development. The goal of this study was to investigate the associations between prenatal depression (EDPS), stress hormones (cortisol), neonatal behavior (NBAS), and brain function (rs-fNIRS) to provide a scientific basis for early detection and intervention.

2. Method

2.1. Participants

This study was a prospective observational study conducted at the First People's Hospital of Foshan, China, from August 2020 to June 2021. The study was approved by the Ethics Committee of Foshan First People's Hospital, and written informed consent were obtained from the participants.

Pregnant women were recruited at their 28–36 weeks' gestation to

participate in this mother-infant dyads study. Maternal inclusion criteria were: 18–45 years old, self-reported good health, and received standard prenatal care. Pregnant women were excluded if they had (1) diseases, including hypertension, heart failure, renal failure, cancer, stroke, or other life-threatening illnesses, or psychiatric disorders (except for depression), (2) history of smoking, drinking, or abusing drugs; or (3) multiple gestations.

Neonatal inclusion criteria: infants born at gestational age (GA) 37 0/7–42 6/7 weeks. Neonatal exclusion criteria: infants with congenital or metabolic diseases, birth weight (BW) $\leq$ 2000 g, Apgar scores $<$ 8 at 1, 5, or 10 min, or admitted to the neonatal intensive care unit (NICU). The flowchart of the cohort study is shown in Fig. 1. Two hundred and twenty pregnant women were recruited; seven mother-infant dyads were excluded due to maternal reasons, and nine mother-infant dyads were excluded because of neonatal illness. A total of 204 mother-infant dyads were included in the study, and the baseline characteristics of the 16 (7.8%) excluded participants did not differ from the included participants. Based on the maternal EPDS score, the mother-infant dyads were divided into the depressed group (EPDS$\geq$10, n = 75) and the control group (EPDS $<$ 10, n = 129). Rs-fNIRS were performed on 134 newborns as 39 mothers declined to test on their infant, although they consented to the testing at the time of enrollment. No testing results were obtained from 23 infants as they did not have a motionless period of $>$ 90 s during the testing. Eight infants had a signal-to-noise ratio of $<$ 1.5 in $>$ 30 % of the measurement fNIRS channels (Kelsey et al., 2021). After propensity matching, data of 21(male = 9) matched infants in each group were used in the fNIRS comparison analysis.

2.2. Procedures

2.2.1. Maternal assessments

Baseline characteristics. All study pregnant women complete baseline data sheets to collect health-related data during the pregnancy, including demographic characteristics (i.e., age, education, and income), medical histories, and pregnancy complications, as well as medical risk factors (i.e., smoking, alcohol drinking, and drug abuse). Gestational age was estimated according to the following methods: early second-trimester ultrasound examination (65.7 %) or the date of the last menstrual period (34.4 %). Pre-pregnancy body mass index (BMI) was computed by using height measured at the time of antenatal care registration and self-reported weight. Prenatal BMI was computed by using the height and weight measured at the time of antenatal care registration.

Maternal Edinburgh Postnatal Depression Scale (EPDS) assessment. Prenatal depressive symptoms were evaluated by the 10 items of the EPDS, a self-report questionnaire (scale range 0–30) extensively adopted to screen for perinatal depression. Higher scores indicate greater depression, with strong specificity and sensitivity (Cox et al., 1987; Smith-Nielsen et al., 2018). A cut-off score of 10 is frequently used to identify individuals who are "at risk" of depression. It has been reported that using a cut-off of 10 in the second and third trimester of pregnancy provides a good balance between sensitivity and specificity (Bergink et al., 2011). This study used EPDS to screen prenatal depressive symptoms in the obstetrics departments, so we selected scores of $\geq$ 10 as the "depressed group". In our study, the participating pregnant women were evaluated twice during their pregnancy; the first assessment was at 28–36 weeks in the outpatient clinics and the second assessment was at 37–42 weeks before delivery after admission to the labor and delivery unit. The average EPDS score from the two assessments was used in the analysis.

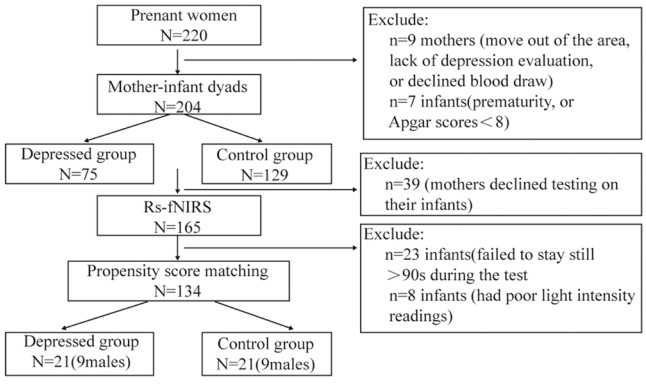


Fig. 1. Flowchart of the enrollment and analysis of the study population. Abbreviation: Resting state-functional near-infrared spectroscopy (fNIRS).

2.2.2. Neonatal assessment

Newborn characteristics, including GA, BW, head circumference, body length, Apgar scores, and medication or treatment, were extracted from medical records.

Neonatal behavioral assessment: the Behavioral Assessment Scale (NBAS) behavioral assessments were administered on the three-day-old newborns by trained researchers who were blind to maternal mental status. When infants were assessed using NBAS, they had arranged in a semi-dark, quiet room at ambient temperatures of 22–27 °C and the assessment between two feeding times.

NBAS is a neurobehavioral scale designed to check infants' (0–2 months of age) responses to a new environment (Brazelton, 1978). It includes 28 behavioral items caused by a series of stimuli and scored on behavioral items in six dimensions: habituation, social–interaction, motor system, state organization, state regulation, and autonomic system dimension. Each dimension contains several subcategories, scoring ranging from 1 to 9 for each subcategory. The scale has adequate reliability (Cronbach's alphas of 0.974) (Başdaş et al., 2018), and higher scores indicate better performance. Our evaluators have received NBAS training, and our program has received a certificate of NBAS implementers from the Brazelton Institute (Harvard Medical School, Boston, MA, USA).

2.2.3. Plasma cortisol measurements

Five ml of maternal peripheral blood was drawn in the morning after they were hospitalized for delivery, and ten ml of umbilical blood was collected immediately after delivery. The blood samples were refrigerated at 4 ℃ before centrifugation, and the plasma samples were stored at − 80 °C. Plasma cortisol concentrations were measured by chemiluminescence analysis using a CLIA kit (Siemens Healthcare Diagnostics Products Limited) that has intra-test and inter-test coefficients of variations $<$ 6 % and $<$ 10 %, respectively. All blood sample processing, storage, and bioassays were performed in the biological laboratory of the Institute of Clinical Research Institute of the First People's Hospital of Foshan. Sample testers were blinded to mother and infant outcomes.

2.2.4. Rs-fNIRS

Data acquisition: Rs-fNIRS testing was performed on three-day-old newborns during natural sleep after being full fed and swaddled. They were scanned in a supine position in a small, quiet testing area. Studies have shown that even when infants are asleep, they will receive sound and light signals, and the corresponding areas of the cerebral cortex will be activated (Wang et al., 2017). We used soft materials for the probes and head cap to make sure the infants' safety and comfort within the fNIRS process. For every infant, the rs-fNIRS data were gathered for approximately 5 mins, with a continuous immobility time of at least 90 s (Geng et al., 2017) (Fig. S1).

All the fNIRS signals were acquired by a multichannel fNIRS system (NirSmart-6000A, Danyang Huichuang Medical Equipment Co., Ltd., China) with two wavelengths (730 and 850 nm) at a sampling rate of 11 Hz. The stretchable head cap covered the prefrontal, temporal, parietal, and occipital lobes. There are 22 sources and 16 detectors (source-detector separation: 2 cm) on the cap, which form 46 measurement

channels. The spatial locations of sources, detectors and anchor points (located at Nz, Cz, Al, Ar, Iz referring to the standard international 10–20 system of electrode placement) were measured by an electromagnetic 3D digitizer device (Patriot, Polhemus, USA) on a model head of newborn. The acquired coordinates were transformed into MNI (Montreal Neurological Institute) coordinates and further projected to the MNI standard brain template using spatial registration approach (Tsuzuki et al., 2007) in NirSpace (Danyang Huichuang Medical Equipment Co., Ltd., China). We define structural brain networks by subdividing the entire brain into eight brain regions based on their locations: the left prefrontal cortex (LPFC), left parietal lobe (LPL), left temporal lobe (LTL), left occipital lobe (LOL), right prefrontal cortex (RPFC), right parietal lobe (RPL), right temporal lobe (RPL) and right occipital lobe (ROL) (Table S1).

fNIRS signal preprocessing: the fNIRS signal preprocessing was conducted using NirSpark software (Danyan, Huichuang, China). In order to reduce the influence of motion artifacts caused by head movement, we conducted spline interpolation to amend motion artifacts. A bandpass filter (0.01–0.1 Hz) was first carried out to divert the noise on the basis of physiological fluctuations such as pulse and respiration. A differential path lengthfactor (DFP) was set to 4 as described in the previous publications (Zee et al., 1992) and (Zhang et al., 2021). And then we used modified Beer–Lambert law (Villringer and Chance, 1997) to calculate the relative changes of in concentrations of oxygen-hemoglobin (HbO) and deoxygen-hemoglobin (HbR). HbO signals were used to test the influence of different hemoglobin concentration signals on the results, because their signal-to-noise ratio was higher than that of HbR signals (Strangman et al., 2002). After defining each fNIRS channel, the functional connections were identified by the functional relationships between node pairs.

3. Statistical analyses

All Statistics are performed using SPSS 25 for Windows (SPSS Inc., Chicago, IL, USA).

We first performed data analysis on the normality distribution of quantitative variables, skewness, and outliers. Continuous variables were expressed by mean ± standard deviation, and categorical variables were expressed by numbers (percentages). First, we analyzed all the variables by univariate analysis. The chi-square test was used to compare the categorical variables, while the Mann-Whitney U test was used to compare the continuous variables. Spearman correlations were used to check correlations between neonatal behavioral assessment outcomes, EPDS, and cortisol levels. We then estimated the effects of cortisol concentrations and EPDS scores on NBAS using linear regression models. Once established the direct relationship between EPDS and neonatal assessment, mediation models were applied to assess whether the relationship between them was mediated by cortisol. Mediation analysis is based on the guidance method proposed by the Preachers and Hayes (Preacher et al., 2007). We adjusted for the covariates to assess for potential mediating effects of cortisol on the relation between EPDS and neonatal assessment. We used SPSS PROCESS for the mediation analysis. Covariables were selected based on mother-infant dyads' univariate analysis results and the published literature. Candidate variables with a p-value of the significant tests < 0.15 on univariate analysis were included in a multivariable model.

To minimize the influences of potential bias on the result of rs-fNIRS, we used a binary logistic-regression model to carry out propensity score matching between the depressed group and the control group (Zishiri et al., 2013). Propensity models included common variables (maternal age, neonatal sex, residence, income, education, type of delivery, parity, and 1-minute Apgar scores). The data of functional connection strength was in normal distribution. Independent sample T test was performed on the mean value of functional connection strength and overall topology changes in each brain region over time series between the depressed group and the control group using NirSpark software. Methods for estimating functional connectivity between network nodes are divided into two steps: Linear Pearson correlation between the temporal signals of paired nodes and Fisher-Z transforming to normalize the correlation values. Then the 46 by 46 connectivity matrix which represents the connection between different node pairs will be obtained from each infant. In this study, the absolute value of the connectivity was used in the entire network analysis since the negative correlation also represents signal synchronism between cortical regions. The topological structure of infants' brain functional network was described by graph theory. In this study, five global network parameters, including normalized clustering coefficient, characteristic path length, global efficiency, local efficiency, and small-world properties were compared between depressed group and control group. We adopted Gretna (Wang et al., 2015) from the MATLAB (US Mathworks) toolbox for each topic to establish the main network analysis of human brain functional networks on the basis of binary brain networks, a variety of sparsity (10 %−50 %, step size = 1 %) to study the relation within sparsity and network performance. Subsequently, 1000 permutations were performed to determine the significance of each component. Correlations among brain functional connectivity (FC) measures and behavioral scores (z-scores) were computed using Pearson's correlation coefficients. All statistical tests were two-sided, $P < 0.05$ was considered statistically significant, and multiple comparisons among channels were considered by the false discovery rate (FDR) correction at $q < 0.05$ for data.

4. Results

4.1. Demographic characteristics and descriptive analysis

We compared the demographic characteristics of mother-infant dyads between the depressed and control groups (Table 1). A total of 204 mother-infant pairs were enrolled in the study, including 75(37%) mothers with depression symptoms (EDPS scores≥10). There was no difference in maternal age, income, education, pre-pregnancy BMI, prenatal BMI, pregnancy desire, parity, and type of delivery between the depressed group and control groups. Covariates (maternal age, prenatal BMI, income and education) with a p value of < 0.15 in this analysis were included in the multivariable model. There was no difference in newborn GA, gender, and 1-minute Apgar scores between the two groups. Compared to the control group, infants in the depress group had lower birth weight ($Z = -2.39$, $p = 0.017$) and smaller head circumference ($Z = -2.36$, $p = 0.018$). Thus, both covariates were included in the regression analysis.

4.2. Maternal prenatal depressive symptoms, NBAS and cortisol

We compared the NBAS scores and cortisol levels between the depressed and control groups (Table S1). Newborns in the depressed group had lower scores on social-interaction ($Z = -7.41$, $p < 0.001$) and autonomic system ($Z = -7.43$, $p < 0.001$) than the control group. However, there was no difference in other NBAS scores (habituation, motor system, state organization, and state regulation) between the two groups ($P > 0.01$). Maternal and cord blood cortisol concentrations were higher in the depressed group than in the control group ($p < 0.001$).

4.3. Correlations among prenatal EPDS, NBAS and cortisol levels

We analyzed correlations among maternal EPDS scores, NBAS scores and cortisol levels (maternal and cord plasma). Bivariate analyses (Table S2) showed that maternal EPDS scores were positively corelated to maternal cortisol levels ($r = 0.171$, $p < 0.05$) and fetal cortisol levels ($r = 0.247$, $p < 0.01$), and negatively correlated to social–interaction ($r = -0.403$, $p < 0.01$) and autonomic system ($r = -0.433$, $p < 0.01$). However, EPDS scores were not associated with other NBAS scores. In the subsequent analyses, we used social-interactive behaviors and the

Table 1
Characteristics of mother-infant dyads in the total sample and subgroups stratified by maternal depressed status in our study.

Variables	Total	Control group (n = 129)	Depressed group (n = 75)	z /X^2	p
Maternal characteristics					
Maternal age (year) Mean ± SD	30.52 ± 3.93	30.9 ± 3.89	29.87 ± 3.94	-1.581	0.114
Pre-pregnancy BMI (kg/m^2) Mean ± SD	21.08 ± 3.08	20.83 ± 3.11	21.50 ± 3.0	-1.32	0.187
Prenatal BMI (kg/m^2) Mean ± SD	26.57 ± 3.65	26.34 ± 3.88	26.95 ± 3.21	-1.59	0.112
Pregnancy desired N (%)				1.07	0.586
accidental pregnancy	42 (20.6)	27 (20.9)	15 (20)		
Spontaneous pregnancy	97 (47.5)	58 (45)	39 (52)		
planned preparation	65 (31.9)	44 (34.1)	21 (28)		
Income level N (%)				4.512	0.105
< 6000 RMB/m/person	38 (18.6)	25 (19.4)	13 (17.3)		
6000–10,000 RMB/m/person	79 (38.7)	43 (33.3)	36 (48)		
≥ 10,000 RMB /m/person	87 (42.6)	61 (47.3)	26 (34.7)		
Education N (%)				4.401	0.111
Lower than high school	32 (15.7)	18 (14.0)	14 (18.7)		
Bachelor's degree	79 (38.7)	45 (34.9)	34 (45.3)		
Higher than bachelor's degree	93 (45.6)	66 (51.2)	27 (36.0)		
Type of delivery N (%)				0.935	0.334
Vaginal delivery	65 (31.9)	38 (29.5)	27 (36)		
Cesarean delivery	139 (68.1)	91 (70.5)	48 (64)		
Parity N (%)				0.089	0.766
Primiparity	87 (42.6)	54 (41.9)	33 (44)		
Multiparity	117 (57.4)	75 (58.1)	42 (56)		
Lives with parents N (%)				0.491	0.484
NO	86 (42.2)	52 (40.3)	34 (45.3)		
Yes	118 (57.8)	77 (59.7)	41 (54.7)		
Neonatal characteristics					
Gestational age (week) Mean ± SD	39.07 ± 0.93	39.14 ± 0.93	38.95 ± 0.93	-1.291	0.197
Gender N (%)				0.506	0.477
Male	110 (53.9)	72 (55.8)	38 (50.7)		
Female	94 (46.1)	57 (44.2)	37 (49.3)		
Apgar scores in 1 min N (%)				1.621	0.445
8	5 (2.5)	2 (1.6)	3 (4)		
9	11 (5.4)	6 (4.7)	5 (6.7)		
10	188 (92.2)	121 (93.8)	67 (89.3)		
Neonatal head circumference (cm) Mean ± SD	34.08 ± 1.01	34.21 ± 0.99	33.85 ± 0.99	-2.356	0.018
Neonatal body length (cm) Mean ± SD	49.08 ± 1.55	49.19 ± 1.58	48.88 ± 1.50	-1.329	0.184
Neonatal weight (kg) Mean ± SD	3.24 ± 0.37	3.28 ± 0.36	3.16 ± 0.38	-2.389	0.017

Abbreviation: NBAS: The Neonatal Behavioral Assessment Scale; BMI: Body mass index.

autonomic system as the behavioral outcomes (Table 2). In the adjusted model (Model 2), maternal EPDS were negatively related to neonatal scores of social–interaction ($\beta = -0.398$, $p < 0.01$) and autonomic system ($\beta = -0.421$, $p < 0.01$). Maternal plasma cortisol levels were not correlated with NBAS sores in social-interaction and autonomic system ($p > 0.05$). Conversely, fetal cortisol levels was negatively correlated to NBAS sores in social–interaction ($\beta = -0.28$, $p < 0.01$) and autonomic system scores ($\beta = -0.309$, $p < 0.01$).

4.4. Mediation analysis between EPDS and NBAS

We analyzed maternal and fetal cortisol levels as potential mediators in the association between EPDS and NBAS (social-interaction and autonomic system). The total effect of EPDS on social-interaction and

Table 2
Hierarchical linear regression analyses predicting NBAS (Social-interaction and Autonomic systems).

	Model 1[1]				Model 2[2]			
	Social-interaction (z)		Autonomic system (z)		Social-interaction (z)		Autonomic system (z)	
	β	95%CI	β	95%CI	β	95%CI	β	95%CI
EPDS (z)	-.399**	-.526,– .272	-.432**	-.557,– .307	-.398**	-.529,– .267	-.421**	-.546,– .295
Maternal Cortisol (z)	-.117	-.255,.021	-.101	-.239,.037	-.129	-.270,.011	-.093	-.230,.045
Fetal Cortisol (z)	-.280**	-.414,– .147	-.306**	-.438,– .174	-.312**	-.449,– .175	-.309**	-.442,– .176

Abbreviation: EPDS: Edinburgh Postnatal Depression Scale; NBAS: The Neonatal Behavioral Assessment Scale.
1. Model 1 was unadjusted.
2. Model 2 was adjusted for maternal age, prenatal BMI, income, education, birth weight and neonatal head circumference.
*$p < 0.05$; **$p < 0.01$; $p > 0.05$ was considered non-significant.
Abbreviation: EPDS: Edinburgh Postnatal Depression Scale; NBAS: The Neonatal Behavioral Assessment Scale.

autonomic system were − 0.398 (−0.529, −0.267; P < 0.001), and − 0.421 (−0.551, −0.289; P < 0.001), respectively (Table S4). Fig. 2 shows that fetal cortisol played a partial negative intermediary role in the relationship between EPDS and social-interaction (β med = −0.054 [−0.12 to 0.018] and autonomic system (β med = −0.052 [−0.105 to 0.019]). The proportional mediation (PM) by fetal cortisol on social interaction and the autonomic system was 13.57 % and 12.33 %, respectively. Maternal cortisol did not act as an intermediary between EPDS and NBAS (social-interaction and autonomic system, p > 0.05).

4.5. Newborn brain functional connectivity

We examined the functional connectivity strength of the whole brain and allopatric brain regions based on HbO signals. Fig. 3A and B shows that the averaged brain FC strength of the depressed group was significantly lower than that in the controlled group (0.38 ± 0.17 vs. 0.52 ± 0.18, t = 2.531, p = 0.039). The differences in brain FC strength in allopatric brain regions between the control group and the depressed groups are shown in Fig. 3 C and D. Compared to the control group, the depressed group had significantly lower cross-interval brain FC intensity in the LPFC- RPFC (t = −3.59 , p = 0.023), LPFC-LPL (t = −3.37, p = 0.023), LPL- LTL (t = −2.86, p = 0.048) and ROL-LPL (t = −3.04, p = 0.039). All p-values are FDR-corrected for multiple comparisons.

4.6. Economic small-world organization

We used graph theory to calculate global network parameters between the depressed and control groups. Fig. 4 summarizes the five global parameters calculated from real brain networks (cool colors) and random networks (warm colors) as a function of sparse thresholds. We found that in the 10–50 % sparsity range, the clustering coefficient (Cp) values and local efficiency of the brain functional networks were greater than the matched random network (Fig. 4A, D), and the path length (Lp) values were comparable to the matched random network (Fig. 4B). The global efficiency of the networks was comparable with the matched random networks (Fig. 4C). While assessing small-world properties, we observed that the small-world values were larger than 1 in the sparsity range of 10 %− 50 % in both two groups (Fig. 4E). However, there were no differences in topological characteristics of the brain network (standardized CP, path length, small-world attribute, global efficiency, as well as local efficiency) between the depressed group and the control group (P > 0.05).

4.7. Relationship between brain connectivity features and NBAS

To test the associations between altered brain functional connectivity features and behavioral characteristics (social-interaction and autonomic system), we conducted a correlation analysis between brain FC and NBAS (social-interaction and autonomic system). We selected 4 brain regions (Fig. 3D, LPFC-RPFC, LPFC-LPL, LPL-LTL and ROL-LPL) where differences in depressed group had been found compared with the control group. Fig. 4 F and G shows the relation between FC Z-score and NBAS Z-score. We found that social-interaction Z-scores were had positive correlations with FC of LPFC-RPFC (r = 0.57, p < 0.01) , LPFC-LPL (r = 0.593, p < 0.01) and LPL-LTL(r = 0.498, p < 0.01), but no correlation with ROL-LPL (r = −0.144, p > 0.05) (Fig. 4F). Autonomic system Z scores were also significantly positive correlation with LPFC-RPFC (r = 0.509, p < 0.01) , LPFC-LPL (r = 0.464, p < 0.01), LPL-LTL (r = 0.381, p < 0.05), and ROL-LPL(r = 0.310, p < 0.05) (Figure4G).

5. Discussion

In this prospective cohort study, we investigated the effect of prenatal depression on NBAS and brain function in three-day-old newborns. NBAS social-interaction and autonomic system performance were negatively correlated to maternal prenatal EPDS scores, suggesting fetal exposure to maternal depression adversely affects brain development and functions. These behavioral changes are partially mediated by fetal, not maternal, plasma cortisol. For the first time, findings from our rs-fNIRS study showed decreased cross-interval brain FC intensity between brain regions (LPFC to RPFC and LPL; LPL to LTL, and ROL-LPL) in newborns with in utero exposure to maternal depression. Furthermore, we found positive correlations between the NBAS Z-scores of social-interaction and autonomic system and strength connecting the brain regions except for ROL-LPL. The topological characteristics of the brain networks were not altered in the infants of depressed mothers.

In this study, we examined the impact of maternal depression in the third trimester, a sensitive period to external signals when the fetal brain has rapid neurites outgrowth and synaptogenesis (Gilmore et al., 2018). Exposure to maternal stress during this time has been linked to future psychological problems (Davis et al., 2011). We have chosen to conduct offspring evaluation on the third day after birth to minimize postnatal maternal depression and other environmental influences. Early postnatal behavioral assessments are essential to identify early signs of abnormal behaviors associated with future neuropsychiatric problems (Räikkönen et al., 2015).

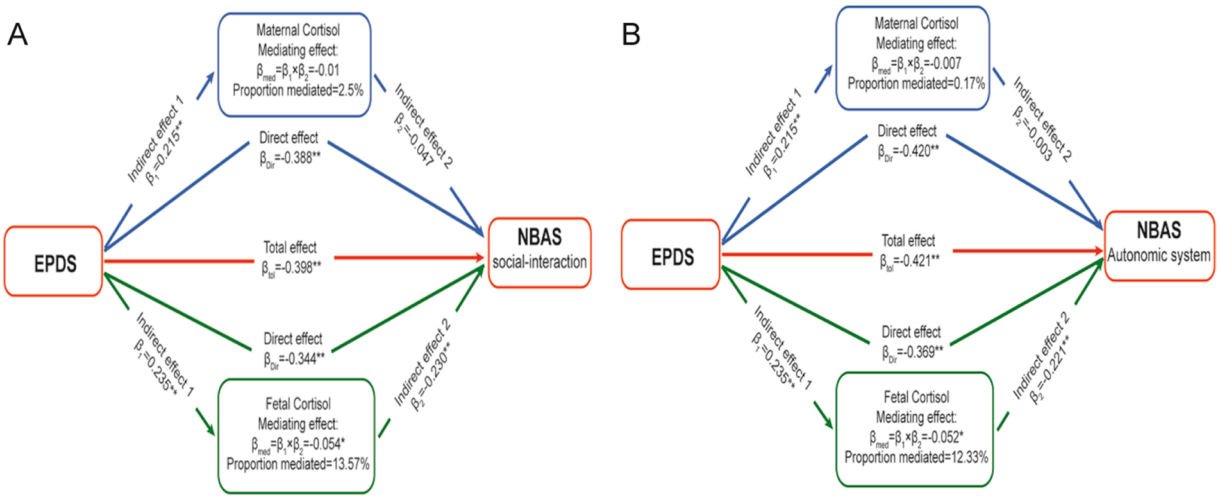


Fig. 2. The contribution of cortisol indicators for the association between EPDS and NBAS. Abbreviation: EPDS: Edinburgh Postnatal Depression Scale; NBAS: The Neonatal Behavioral Assessment Scale. A: Social-Interaction , B: Autonomic system *p < 0.05; **p < 0.01.

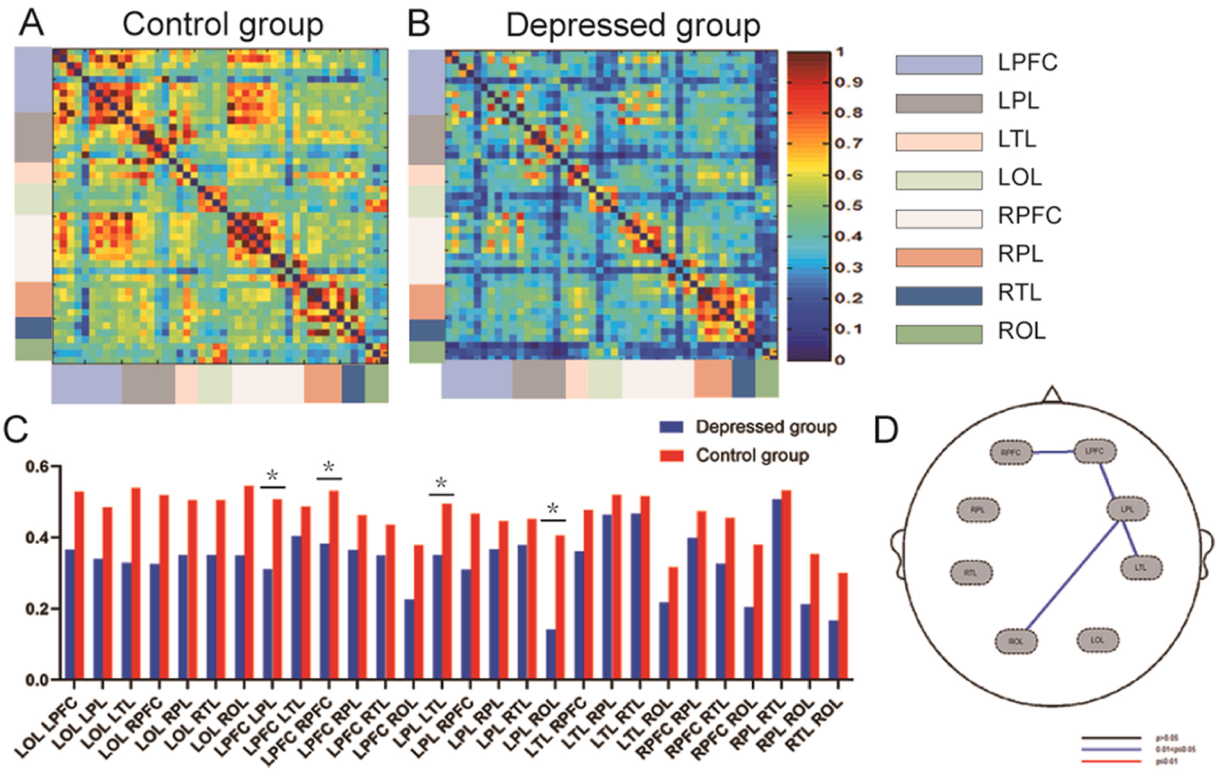


Fig. 3. Characteristics and differences of whole brain functional connectivity between depressed group and control group based on HbO. Abbreviation: left prefrontal cortex (LPFC), left parietal lobe (LPL), left temporal lobe (LTL), left occipital lobe (LOL), right prefrontal cortex (RPFC), right parietal lobe (RPL), right temporal lobe (RPL) and right occipital lobe (ROL). *p < 0.05; * *p < 0.01; p > 0.05 was considered non-significant.

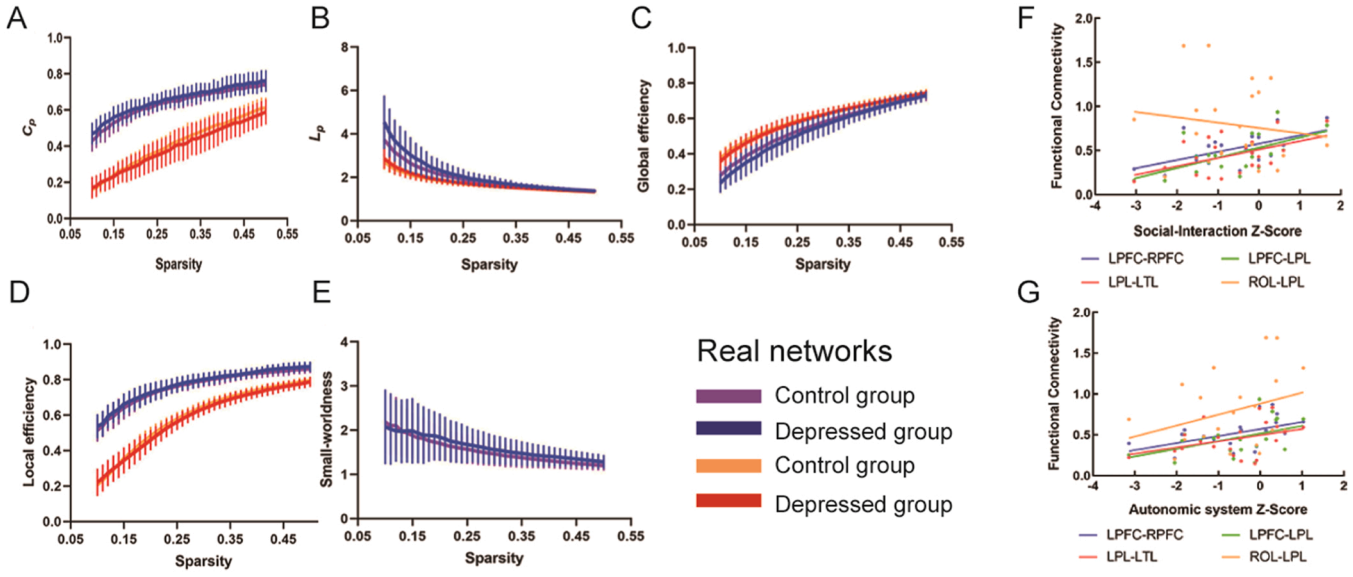


Fig. 4. Global network metrics in a range of sparsity thresholds and correlation between NBAS and functional connectivity coefficient of brain. The clustering coefficient, (B) the characteristic path length, (C) The small-worldness, (D) Global efficiency, (E) local efficiency. Error bars (A, B, C, D) correspond to the standard errors of the mean for 1000 comparable random null networks. Error bars in (E) indicate the standard errors in all subjects. Abbreviation: left prefrontal cortex (LPFC), left parietal lobe (LPL), left temporal lobe (LTL), left occipital lobe (LOL), right prefrontal cortex (RPFC), right parietal lobe (RPL), right temporal lobe (RPL) and right occipital lobe (ROL).

5.1. Influences of prenatal depressive symptoms on neonatal behavioral development

This study showed that newborns of mothers with prenatal depression showed low scores in NBAS social interaction scores and autonomic system. This finding is consistent with previous studies that infants of prenatal depressive mothers had low NBAS scores. However, the previous studies observed poor performance in additional domains; habituation, motor system, and state regulation(Gerardin et al., 2011, Figueiredo et al., 2017, Zhang et al., 2017, Osborne et al., 2018). The

discrepancies might be related to the study differences in severity of maternal depression and the timing of offspring evaluation. Lower scores on the social-interaction suggest that the affected newborns are less capable of expressing internal states and communicating with their parents like a typically developed newborn (Rosenstein and Oster, 1988). Lower scores on the autonomic system indicate a poor parasympathetic regulation of homeostatic stress due to a delay in neurobehavioral maturity (Field and Diego, 2008, Figueiredo et al., 2017).

5.2. Mediating effects of cortisol

In line with the literature, we observed increased cortisol levels in depressed mothers and their fetuses. However, we found that only fetal cortisol partially regulated neonatal behavior development. Cortisol in the fetal circulation is a combination produced endogenously by the fetus and derived from the mother and placenta (Bergman et al., 2010). Although liposoluble steroids easily cross the placenta, fetal cortisol levels are significantly lower than maternal circulating levels. The active cortisol is covered to the inert 11-ketone form (cortisone) by the placental 11β-HSD2 (Chapman, Holmes et al., 2013). The balance between maternal cortisol and offspring cortisol is also regulated by placenta-related genes, such as corticotrophin-releasing hormone (CRH), 11β-HSD2, and glucocorticoid receptor (GR) (Yehuda et al., 2014; Bowers and Yehuda, 2016; Joseph and Whirledge, 2017). Altered cortisol levels are thought to affect the development of fetal brain regions, including the limbic and frontotemporal networks (Lautarescu et al., 2020). While our results showed a mediating role of fetal cortisol, it only accounted for 13 % of the total effect. Other mediating factors remain to be determined.

5.3. Effects of prenatal depression on brain functional connectivity and brain network in neonates

In this study, rs-fNIRS was used to explore the characteristics and differences of functional connectivity of cortical brain networks between the prenatal depressed group and the control group. The results showed that the FC intensity of the depressed group was lower than that of the control group. It haven been shown that maternal stress, depression, and anxiety, even if they do not reach the severity levels of mental disorders, are related to changes in fetal brain structure and function (Wu et al., 2020). Our results showed that the strength of the left frontal-parietal network connection was decreased in the depressed group. The NBAS (social-interaction and autonomic system) Z scores were positively correlated with prefrontal-frontal connectivity. The cognitive ability of normal people is positively related to the functional connection between the frontal-parietal lobe. fMRI studies have shown that cognitive training, such as working memory, enhances the FC in the frontal-parietal lobe (Cole et al., 2012, Jolles et al., 2013). We also found reduced FC strength in temporal-parietal connection in infants of depressed mothers, which positively correlated to their NBAS Z-scores (social-interaction and autonomic system. Nichola et al. have shown that temporal-parietal connection is involved in informing the internal link of sensory-action relationships (DiQuattro et al., 2014). Recent studies have indicated that the activation of the temporal-parietal junction is related to functions involving social cognition, episodic memory retrieval, and attention redirection (Igelström and Graziano, 2017). Bulgarelli et al. (2019) have shown that infants with a good sense of self have increased functional connectivity between the frontal and temporal-parietal regions.

We compared the topological organization of neonatal brain functional connectivity between the infants in the prenatal depressed group and the control group. The brain functional networks of the two groups showed comparable economic small-world organization, global efficiency, and local efficiency. Global (whole) and local (node-specific) network properties are usually adopted to represent the developing brain's integration and separation. Our results suggested that maternal prenatal depression has no significant effect on the development of integration and separation in offspring brain networks. The existing research on infants indicates that functional connectivity in higher-order cortical networks across longer ranges involving the frontal, temporal, and parietal cortex shows more protracted development during infancy (Gao et al., 2015). Different functional systems have distinct developmental trajectories. The maturation trajectories follow such orders: from the primary functional systems, the temporal and parietal association cortices (e.g., those mediating language and spatial attention), and then to the higher cognitive functional systems (e.g., social cognition and executive control) (Gao et al., 2015; Ouyang et al., 2017; Liu et al., 2008; A, B et al., 2008; Lin et al., 2008; Gao et al., 2014; Gao et al., 2015; Ouyang et al., 2017). Spatially, the maturing patterns start from posterior to anterior regions, from inferior to superior areas, and from medial to lateral regions (Gao et al., 2014). Most higher-order association cortices and their projections to the subcortical areas have protracted maturation processes (Zhang et al., 2017). Early post-natal development is a critical period for brain maturation and synapse remodeling (Brioschi et al., 2020) and it has been a sensitive period for the full development of social-emotional abilities (Vanderwert et al., 2010).

5.4. Limitations

This study has several limitations. First, although we evaluated the mediating role of maternal and fetal cortisol levels on the relation between EPDS and NBAS scores, some confounding factors (low birth weight, low head circumference) may be potential mediators in the analysis. Second, we performed maternal EPDS evaluation in the third trimester. However, we cannot determine if our observations are specific to the third trimester as they may be the results of continued exposure during pregnancy. Third, we performed neonatal behavior assessment at a single time point. Multiple evaluations might increase the power of the study. In addition, studies have recommended that measuring again after seven weeks of life would have better neurobehavioral performance than 1-week-old infants (Costa et al., 2010). However, it might be associated with an increased influence of postpartum maternal depression. Finally, this observational study does not lead to a causal relationship. Therefore, the conclusions drawn from the current study are preliminary and need to be replicated in different and larger cohorts.

6. Conclusions

Prenatal exposure to maternal depression is associated with delayed or altered development of neonatal social-interaction, autonomic system, and brain functional connectivity strength. Prenatal depression has significant implications on maternal and offspring's mental health. Prenatal screening for maternal depression and early postnatal behavioral evaluation provides the opportunity for early diagnosis and intervention to improve neurodevelopmental outcomes.

Submission declaration

I declare that the work described has not been published previously even partially, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Acknowledgements

This work was supported by the National Natural Science Foundation of China [No. 81873805]. The person in charge is Hui Li.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105896.

References

Anderson, J.S., Nielsen, J.A., Froehlich, A.L., DuBray, M.B., Druzgal, T.J., Cariello, A.N., Cooperrider, J.R., Zielinski, B.A., Ravichandran, C., Fletcher, P.T., Alexander, A.L., Bigler, E.D., Lange, N., Lainhart, J.E., 2011. Functional connectivity magnetic resonance imaging classification of autism. Brain 134 (12), 3742–3754.

Başdaş, Ö., Erdem, E., Elmalı, F., Kurtoğlu, S., 2018. The Brazelton neonatal behavioral assessment scale: a validity and reliability study in a Turkish sample. Turk. J. Med. Sci. 48 (2), 399–404.

Beijers, R., Buitelaar, J.K., de Weerth, C., 2014. Mechanisms underlying the effects of prenatal psychosocial stress on child outcomes: beyond the HPA axis. Eur. Child Adolesc. Psychiatry 23 (10), 943–956.

Benavides-Varela, S., Gómez, D.M., Mehler, J., 2011. Studying neonates' language and memory capacities with functional near-infrared spectroscopy. Front. Psychol. 2, 64.

Bergink, V., Kooistra, L., Lambregtse-van den Berg, M.P., Wijnen, H., Bunevicius, R., van Baar, A., Pop, V., 2011. Validation of the Edinburgh Depression Scale during pregnancy. J. Psychosom. Res. 70 (4), 385–389.

Bergman, K., Sarkar, P., Glover, V., O'Connor, T.G., 2010. Maternal prenatal cortisol and infant cognitive development: moderation by infant-mother attachment. Biol. Psychiatry 67 (11), 1026–1032.

Bowers, M.E., Yehuda, R., 2016. Intergenerational transmission of stress in humans. Neuropsychopharmacology 41 (1), 232–244.

Brazelton, T.B., 1978. The Brazelton neonatal behavior assessment scale: introduction. Monogr. Soc. Res. Child Dev. 43 (5–6), 1–13.

Brioschi, S., d'Errico, P., Amann, L.S., Janova, H., Wojcik, S.M., Meyer-Luehmann, M., Rajendran, L., Wieghofer, P., Paolicelli, R.C., Biber, K., 2020. Detection of synaptic proteins in microglia by flow cytometry. Front. Mol. Neurosci. 13, 149.

Bulgarelli, C., Blasi, A., de Klerk, C., Richards, J.E., Hamilton, A., Southgate, V., 2019. Fronto-temporoparietal connectivity and self-awareness in 18-month-olds: a resting state fNIRS study. Dev. Cogn. Neurosci. 38, 100676.

Cai, L., Dong, Q., Niu, H., 2018. The development of functional network organization in early childhood and early adolescence: a resting-state fNIRS study. Dev. Cogn. Neurosci. 30, 223–235.

Caparros-Gonzalez, R.A., Romero-Gonzalez, B., Gonzalez-Perez, R., Lucena-Prieto, L., Perez-Garcia, M., Cruz-Quintana, F., Peralta-Ramirez, M.I., 2019. Maternal and neonatal hair cortisol levels are associated with infant neurodevelopment at six months of age. J. Clin. Med. 8, 11.

Cole, M.W., Yarkoni, T., Repovs, G., Anticevic, A., Braver, T.S., 2012. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. J. Neurosci. 32 (26), 8988–8999.

Costa, R., Figueiredo, B., Tendais, I., Conde, A., Pacheco, A., Teixeira, C., 2010. Brazelton neonatal behavioral assessment scale: a psychometric study in a Portuguese sample. Infant Behav. Dev. 33 (4), 510–517.

Cox, J.L., Holden, J.M., Sagovsky, R., 1987. Detection of postnatal depression. Development of the 10-item Edinburgh postnatal depression scale. Br. J. Psychiatry 150, 782–786.

Davis, E.P., Glynn, L.M., Waffarn, F., Sandman, C.A., 2011. Prenatal maternal stress programs infant stress regulation. J. Child Psychol. Psychiatry 52 (2), 119–129.

DiPietro, J.A., Costigan, K.A., Voegtline, K.M., 2015. Studies in fetal behavior: revisited, renewed, and reimagined. Monogr. Soc. Res. Child Dev. 80 (3), 1–94.

DiQuattro, N.E., Sawaki, R., Geng, J.J., 2014. Effective connectivity during feature-based attentional capture: evidence against the attentional reorienting hypothesis of TPJ. Cereb. Cortex 24 (12), 3131–3141.

Edde, M., Leroux, G., Altena, E., Chanraud, S., 2021. Functional brain connectivity changes across the human life span: from fetal development to old age. J. Neurosci. Res. 99 (1), 236–262.

Field, T., Diego, M., 2008. Vagal activity, early growth and emotional development. Infant Behav. Dev. 31 (3), 361–373.

Field, T., Diego, M., Hernandez-Reif, M., 2006. Prenatal depression effects on the fetus and newborn: a review. Infant Behav. Dev. 29 (3), 445–455.

Figueiredo, B., Pinto, T.M., Pacheco, A., Field, T., 2017. Fetal heart rate variability mediates prenatal depression effects on neonatal neurobehavioral maturity. Biol. Psychol. 123, 294–301.

Figueiredo, B., Pacheco, A., Costa, R., Conde, A., Teixeira, C., 2010. Mother's anxiety and depression during the third pregnancy trimester and neonate's mother versus stranger's face/voice visual preference. Early Hum. Dev. 86 (8), 479–485.

Gao, W., Alcauter, S., Smith, J.K., Gilmore, J.H., Lin and Function, W.J.B.S., 2015. Development of human brain cortical network architecture during infancy. Brain Struct Funct 220 (2), 1173–1186.

Gao, W., Alcauter, S., Smith, J.K., Gilmore, J.H., Lin, W., 2015. Development of human brain cortical network architecture during infancy. Brain Struct. Funct. 220 (2), 1173–1186.

Gao, W., Sarael, A., Amanda, E., Hernandez-Castillo, C.R., Keith, S.J., Juanita, R., Lin, W. J. C.C., 2014. Functional network development during the first year: relative sequence and socioeconomic correlations (9): 9.

Geng, S., Liu, X., Biswal, B.B., Niu, H., 2017. Effect of resting-state fNIRS scanning duration on functional brain connectivity and graph theory metrics of brain network. Front. Neurosci. 11, 392.

Gerardin, P., Wendland, J., Bodeau, N., Galin, A., Bialobos, S., Tordjman, S., Mazet, P., Darbois, Y., Nizard, J., Dommergues, M., Cohen, D., 2011. Depression during pregnancy: is the developmental impact earlier in boys? A prospective case-control study. J. Clin. Psychiatry 72 (3), 378–387.

Gilmore, J.H., Knickmeyer, R.C., Gao, W., 2018. Imaging structural and functional brain development in early childhood. Nat. Rev. Neurosci. 19 (3), 123–137.

Graham, R.M., Jiang, L., McCorkle, G., Bellando, B.J., Sorensen, S.T., Glasier, C.M., Ramakrishnaiah, R.H., Rowell, A.C., Coker, J.L., Ou, X., 2020. Maternal anxiety and depression during late pregnancy and newborn brain white matter development. AJNR Am. J. Neuroradiol. 41 (10), 1908–1915.

Hu, Z., Liu, G., Dong, Q., Niu, H., 2020. Applications of resting-state fNIRS in the developing brain: a review from the connectome perspective. Front. Neurosci. 14, 476.

Igelström, K.M., Graziano, M.S.A., 2017. The inferior parietal lobule and temporoparietal junction: a network perspective. Neuropsychologia 105, 70–83.

Jolles, D.D., van Buchem, M.A., Crone, E.A., Rombouts, S.A., 2013. Functional brain connectivity at rest changes after working memory training. Hum. Brain Mapp. 34 (2), 396–406.

Joseph, D.N., Whirledge, S., 2017. Stress and the HPA axis: balancing homeostasis and fertility. Int. J. Mol. Sci. 18, 10.

Kelsey, C.M., Farris, K., Grossmann, T., 2021. Variability in infants' functional brain network connectivity is associated with differences in affect and behavior. Front. Psychiatry 12, 685754.

Keunen, K., Counsell, S., Benders, M., 2017. The emergence of functional architecture during early brain development. NeuroImage 160, 2–14.

Lautarescu, A., Craig, M.C., Glover, V., 2020. Prenatal stress: effects on fetal and child brain development. Int. Rev. Neurobiol. 150, 17–40.

Lebel, C., Walton, M., Letourneau, N., Giesbrecht, G.F., Kaplan, B.J., Dewey, D., 2016. Prepartum and postpartum maternal depressive symptoms are related to children's brain structure in preschool. Biol. Psychiatry 80 (11), 859–868.

Lin, W., Zhu, Q., Gao, W., Chen, Y., Toh, C.H., Styner, M., Gerig, G., Smith, J.K., Biswal, B., Gilmore, J.H., 2008. Functional connectivity MR imaging reveals cortical functional connectivity in the developing brain. AJNR Am J Neuroradiol 29 (10), 1883–1889.

Madigan, S., Oatley, H., Racine, N., Fearon, R.M.P., Schumacher, L., Akbari, E., Cooke, J. E., Tarabulsy, G.M., 2018. A meta-analysis of maternal prenatal depression and anxiety on child socioemotional development. J. Am. Acad. Child Adolesc. Psychiatry 57 (9), 645–657 e648.

Morsi, A., DeFranco, D., Witchel, S.F., 2018. The hypothalamic-pituitary-adrenal axis and the fetus. Horm. Res. Paediatr. 89 (5), 380–387.

O'Donnell, K.J., Meaney, M.J., 2017. Fetal origins of mental health: the developmental origins of health and disease hypothesis. Am. J. Psychiatry 174 (4), 319–328.

Osborne, S., Biaggi, A., Chua, T.E., Du Preez, A., Hazelgrove, K., Nikkheslat, N., Previti, G., Zunszain, P.A., Conroy, S., Pariante, C.M., 2018. Antenatal depression programs cortisol stress reactivity in offspring through increased maternal inflammation and cortisol in pregnancy: the psychiatry research and motherhood - depression (PRAM-D) study. Psychoneuroendocrinology 98, 211–221.

Ouyang, M., Kang, H., Detre, J.A., Roberts, T.P.L., Huang, H., 2017. Short-range connections in the developmental connectome during typical and atypical brain maturation. Neurosci. Biobehav. Rev. 83, 109–122.

Ouyang, M., Kang, H., Detre, J.A., Roberts, T.P.L., Huang, H.J.N., Reviews, B., 2017. Short-range connections in the developmental connectome during typical and atypical brain maturation. S0149763417303767.

Pacheco, A., Figueiredo, B., 2012. Mother's depression at childbirth does not contribute to the effects of antenatal depression on neonate's behavioral development. Infant Behav. Dev. 35 (3), 513–522.

Posner, J., Cha, J., Roy, A.K., Peterson, B.S., Bansal, R., Gustafsson, H.C., Raffanello, E., Gingrich, J., Monk, C., 2016. Alterations in amygdala-prefrontal circuits in infants exposed to prenatal maternal depression. Transl. Psychiatry 6 (11), e935.

Preacher, K.J., Rucker, D.D., Hayes, A.F., 2007. Addressing moderated mediation hypotheses: theory, methods, and prescriptions. Multivar. Behav. Res. 42 (1), 185–227.

Qiu, A., Anh, T.T., Li, Y., Chen, H., Rifkin-Graboi, A., Broekman, B.F., Kwek, K., Saw, S. M., Chong, Y.S., Gluckman, P.D., Fortier, M.V., Meaney, M.J., 2015. Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. Transl. Psychiatry 5 (2), e508.

Räikkönen, K., Pesonen, A.K., O'Reilly, J.R., Tuovinen, S., Lahti, M., Kajantie, E., Villa, P., Laivuori, H., Hämäläinen, E., Seckl, J.R., Reynolds, R.M., 2015. Maternal depressive symptoms during pregnancy, placental expression of genes regulating glucocorticoid and serotonin function and infant regulatory behaviors. Psychol. Med. 45 (15), 3217–3226.

Rosenstein, D., Oster, H., 1988. Differential facial responses to four basic tastes in newborns. Child Dev. 59 (6), 1555–1568.

Ruisch, I.H., Buitelaar, J.K., Glennon, J.C., Hoekstra, P.J., Dietrich, A., 2018. Pregnancy risk factors in relation to oppositional-defiant and conduct disorder symptoms in the avon longitudinal study of parents and children. J. Psychiatr. Res. 101, 63–71.

Seckl, J.R., Holmes, M.C., 2007. Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. Nat. Clin. Pract. Endocrinol. Metab. 3 (6), 479–488.

Smith-Nielsen, J., Matthey, S., Lange, T., Væver, M.S., 2018. Validation of the Edinburgh postnatal depression scale against both DSM-5 and ICD-10 diagnostic criteria for depression. BMC Psychiatry 18 (1), 393.

Smyser, C.D., Snyder, A.Z., Shimony, J.S., Blazey, T.M., Inder, T.E., Neil, J.J., 2013. Effects of white matter injury on resting state fMRI measures in prematurely born infants. PLOS One 8 (7), e68098.

Strangman, G., Culver, J.P., Thompson, J.H., Boas, D.A., 2002. A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage 17 (2), 719–731.
Tsuzuki, D., Jurcak, V., Singh, A.K., Okamoto, M., Watanabe, E., Dan, I., 2007. Virtual spatial registration of stand-alone fNIRS data to MNI space. Neuroimage 34 (4), 1506–1518.
Tuovinen, S., Lahti-Pulkkinen, M., Girchenko, P., Lipsanen, J., Lahti, J., Heinonen, K., Reynolds, R.M., Hämäläinen, E., Kajantie, E., Laivuori, H., Pesonen, A.K., Villa, P.M., Räikkönen, K., 2018. Maternal depressive symptoms during and after pregnancy and child developmental milestones. Depress. Anxiety 35 (8), 732–741.
Turk, E., van den Heuvel, M.I., Benders, M.J., de Heus, R., Franx, A., Manning, J.H., Hect, J.L., Hernandez-Andrade, E., Hassan, S.S., Romero, R., Kahn, R.S., Thomason, M.E., van den Heuvel, M.P., 2019. Functional connectome of the fetal brain. J. Neurosci. 39 (49), 9716–9724.
Van den Bergh, B.R.H., van den Heuvel, M.I., Lahti, M., Braeken, M., de Rooij, S.R., Entringer, S., Hoyer, D., Roseboom, T., Räikkönen, K., King, S., Schwab, M., 2020. Prenatal developmental origins of behavior and mental health: the influence of maternal stress in pregnancy. Neurosci. Biobehav. Rev. 117, 26–64.
Vanderwert, R.E., Marshall, P.J., Nelson 3rd, C.A., Zeanah, C.H., Fox, N.A., 2010. Timing of intervention affects brain electrical activity in children exposed to severe psychosocial neglect. PLOS One 5 (7), e11415.
Villringer, A., Chance, B., 1997. Non-invasive optical spectroscopy and imaging of human brain function. Trends Neurosci. 20 (10), 435–442.
Wang, J., Dong, Q., Niu, H., 2017. The minimum resting-state fNIRS imaging duration for accurate and stable mapping of brain connectivity network in children. Sci. Rep. 7 (1), 6461.
Wang, J., Wang, X., Xia, M., Liao, X., Evans, A., He, Y., 2015. GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. Front. Hum. Neurosci. 9, 386.
Wen-Ching, L., Flax, J.F., Guise, K.G., Sukul, V., Benasich, A.A., 2008. Functional connectivity of the sensorimotor area in naturally sleeping infants. Brain Res. 1223 (1), 42–49.
Wu, Y., Lu, Y.C., Jacobs, M., Pradhan, S., Kapse, K., Zhao, L., Niforatos-Andescavage, N., Vezina, G., du Plessis, A.J., Limperopoulos, C., 2020. Association of prenatal maternal psychological distress with fetal brain growth, metabolism, and cortical maturation. JAMA Netw. Open 3 (1), e1919940.
Yehuda, R., Daskalakis, N.P., Lehrner, A., Desarnaud, F., Bader, H.N., Makotkine, I., Flory, J.D., Bierer, L.M., Meaney, M.J., 2014. Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. Am. J. Psychiatry 171 (8), 872–880.
Zee, P., Cope, M., Arridge, S., Essenpreis, M., Potter, L., Edwards, A., Wyatt, J., McCormick, D., Roth, S., Reynolds, E., 1992. Experimentally measured optical pathlengths for the adult head, calf and forearm and the head of the newborn infant as a function of inter optode spacing. Oxygen Transport to Tissue XIII. Springer,, pp. 143–153.
Zhang, H., Su, Q., Yao, D., Wang, S., Dang, S., Ding, D., Zhu, Z., Shao, S., Li, H., 2017. Prolactin, a potential mediator of reduced social interactive behavior in newborn infants following maternal perinatal depressive symptoms. J. Affect Disord. 215, 274–280.
Zhang, H., Yin, W., Lin, W., Shen, D., 2017. The developing triple networks in infants from 2-week-old to 2-year-old: a longitudinal study, OHBM.
Zhang, S., Peng, C., Yang, Y., Wang, D., Li, D.J. N., 2021. Resting-state brain networks in neonatal hypoxic-ischemic brain damage: a functional near-infrared spectroscopy study. 8(2).
Zishiri, E.T., Williams, S., Cronin, E.M., Blackstone, E.H., Ellis, S.G., Roselli, E.E., Smedira, N.G., Gillinov, A.M., Glad, J.A., Tchou, P.J., Szymkiewicz, S.J., Chung, M. K., 2013. Early risk of mortality after coronary artery revascularization in patients with left ventricular dysfunction and potential role of the wearable cardioverter defibrillator. Circ. Arrhythm. Electrophysiol. 6 (1), 117–128.